spotlights

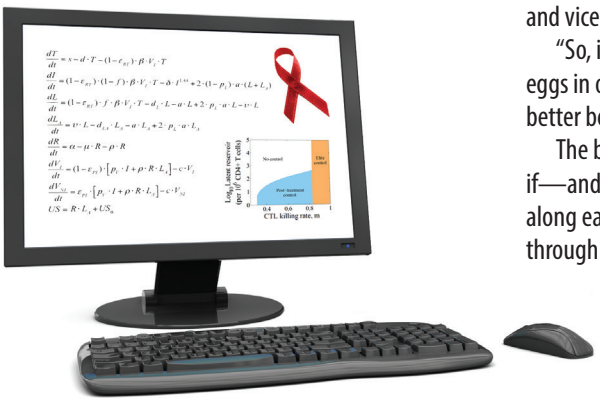
Fit for a Cure

In his work toward understanding the infection dynamics of HIV, the Laboratory's Alan Perelson works exclusively with model patients. Literally. He builds computer models of HIV infection to help make sense of puzzling clinical data.

When asked whether he is a virologist or a mathematician, Perelson quips, "Yes." Pressed for more, he clarifies, "I am a mathematical modeler of viral systems and immune processes."

Experimental and clinical studies provide the numbers, such as the number of HIV-susceptible cells in a volume of blood or the average number of viruses circulating in the blood. Perelson takes those numbers and devises complex mathematical equations to describe their relationships to one another, then fits his model to the data. If it's a good fit, he can illuminate portions of the virus-host relationship that are otherwise murky. And during the past year, his team has made some compelling new discoveries.

When a French study reported that a dozen or so patients had quit antiviral drug therapy yet maintained undetectable virus levels—representing a functional cure to an incurable disease—Perelson wanted to know why. If researchers can understand how that happened, then clinicians might be able to help more patients achieve a functional cure. Perelson and postdoctoral researcher Jessica Conway hatched a theory that these patients, who had each been diagnosed and treated very soon after infection, had in so doing given their immune systems a leg up, which kept down the number of viruses in their blood.



By including immune cells in their model, Perelson and Conway determined that an early diagnosis and prompt initiation of treatment can lead to a smaller "latent reservoir"—a hidden population of infected cells. These cells, as long as they aren't producing more viruses, are invisible to the immune system. But they can become active later and suddenly begin producing viruses. The more cells there are in the latent reservoir, the harder it is for the immune response to contain them once they start producing viruses. Very early treatment for the study patients capped their virus numbers at low levels, keeping their latent reservoirs small, thus allowing their immune systems a chance to get ahead of the infection.

The next question Perelson wanted to answer had to do with the nature of the immune response. Certain types of antibodies, called broad neutralizing antibodies (BnAbs), are effective at preventing the spread of infection from one cell to the next. But because BnAbs only appear years into an HIV infection, their utility is usually handily overwhelmed by the virus. Perelson wanted to find a way to make BnAbs appear early in the infection, when they can do the most good.

To do this, he and postdoctoral researcher Shishi Luo built a model of virus-antibody coevolution. HIV mutates liberally to evade neutralization by antibodies. Similarly, the immune system uses mutation to produce a spectrum of antibodies in hopes that some of them will be strongly matched to the virus. The result is an evolutionary arms race with both sides trying to stay nimble while casting a wide net. The model revealed that antibody production is a zero-sum game, with BnAbs coming at a cost to other types of antibodies and vice versa.

"So, if you're going to put all your antibody eggs in one basket," Perelson says, "it had better be the right basket."

The best antibody basket is indeed BnAbs if—and it's a big "if"—the BnAbs come along early enough. The way to do that is through viral genetic diversity. More variation early on—say, from an intentionally diverse vaccine preparation—leads to more BnAbs sooner, shifting the infection dynamic in favor of the host.

But Perelson isn't concentrating solely on the host response. Recently he and postdoctoral researcher Ruian Ke, along with several external collaborators, have been exploring ways of working the other side of the arms race: the latent reservoir, that sleeper cell of sleeper cells. A popular strategy, dramatically called "shock and kill," attempts to first stimulate latently infected cells into becoming productive and then target them for destruction. Recent clinical results from a latency-reversing agent (LRA) called Vorinostat were inconsistent, with varying extents and durations of activation. Perelson's task was again to suss out why such variation occurred and also to quantify the impact of Vorinostat. The model that fit the clinical data put LRA-activated cells into a different category than ordinary virus-producing cells and also allowed them to return to latency after a period of time, which makes Vorinostat less an agent of "shock and kill" and more one of "surprise and confuse."

So Vorinostat turns out to be a lackluster LRA. But when new, better LRAs come along, Perelson and his models will be set to crunch the numbers. Since drug discovery and clinical trials take years, it's a relief to know that, for model patients at least, a cure may be just a few clicks away.

—Eleanor Hutterer

Nuclear War Against Cancer

Exposure to nuclear radiation causes cancer—and sometimes cures it. But radiation, like chemotherapy, can be an indiscriminate killer, attacking cancerous and healthy cells alike. The damage to healthy cells can be quite widespread, which is why the prospect of cancer treatment often generates apprehension nearly on par with the cancer itself.

However, a treatment called radioimmunotherapy (RIT) delivers specialized, radioactive isotopes, or radioisotopes, directly to cancerous tumors within a patient's body. There, cell-killing radiation from the radioisotope bombards cancer cells while minimizing damage to the surrounding healthy tissue.

The key to success is multi-pronged, requiring the ideal radioisotope to obliterate the tumor, a biological delivery system to get it there, and a specialized molecule that holds the radioisotope tightly within the delivery system.

RIT targets cancer cells that express a distinctive antigen on their outer surfaces. An antibody specific to that antigen is attached to the radioisotope, and when the antibody encounters its antigen, that means the medicine has reached the tumor, even if tumors are scattered all over the body. Not all cancers produce a distinctive antigen for targeting, and therefore not all cancers can be treated with RIT, but those that do include heavy hitters such as prostate cancer, colorectal cancer, melanoma (skin), leukemia (bone marrow), and non-Hodgkins lymphoma (blood). Finding suitable antibodies to deliver the radioisotopes is a major challenge, and it is likely that better antigens to target have yet to be discovered, but several successful antibodies have already been demonstrated.

Eva Birnbaum runs the Los Alamos program for isotope production and applications, and Kevin John leads the national tri-lab isotope effort, which engages the Los Alamos, Oak Ridge, and Brookhaven national laboratories to produce RIT isotopes. While other researchers work to refine the antibodies, Birnbaum and John focus on finding and demonstrating the most effective radioisotope for treatment—and then making a lot of it.

"The optimal radioisotope needs to do two almost contradictory things," John explains. "It has to deliver a powerful dose of radiation to kill the tumor completely—without damaging healthy tissue in the immediate vicinity of the tumor and without lingering too long in the patient's system. It has to show up, do its job, and then go away."

Birnbaum and John believe the tri-lab team has found its winner with the isotope actinium-225, which undergoes radioactive decay by emitting an alpha particle. Being far more massive than the particles produced by any other form of radioactivity, alpha particles are released with high energy and relatively slow speed. As a result, they deliver a powerful punch in a short distance—typically only a few cell diameters—thereby affecting the tumor cells but not many of the surrounding healthy cells.

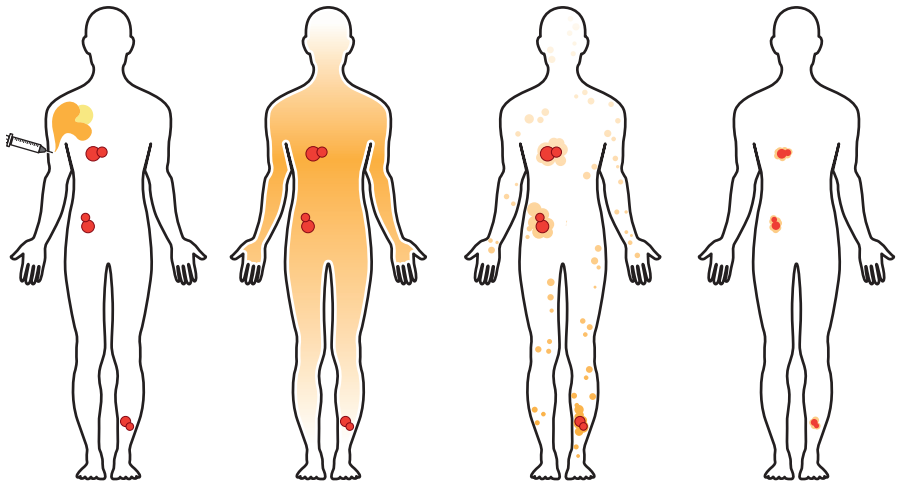
Actinium-225 also has the benefit that, after its nucleus decays by expelling an alpha particle, what's left behind is no longer actinium-225 but francium-221, which is also an alpha emitter. So, too, are the next two decay products—four alpha particles for every atom of actinium-225. So a little goes a long way. "The four alphas are especially important," Birnbaum says. "It's like repeated hammer blows in the same spot. After the initial hit, each successive impact multiplies the damage."

Additionally, actinium-225 has a half-life of just ten days—long enough that most of the administered dose has time to reach the tumor before decaying but short enough that very little of it lingers in a patient's body in the months following treatment. (Francium and its decay products have a half-life of only minutes or seconds.) The short timescale in which the isotope's powerful four-alpha radiation dose is concentrated and its subsequent radiological inertness are what make actinium-225 such an ideal nuclear weapon against cancer.

Because of its brief half-life, actinium-225 cannot be found in nature and must be made in a laboratory. Los Alamos and Brookhaven are doing so with their powerful proton-accelerator beams trained on a thorium target, resulting in a variety of radioisotopes, including actinium-225. Scientists then apply a series of chemistry-based purification methods to isolate the actinium from the other elements produced. It might sound straightforward, but the details matter. The targets have to be designed to withstand irradiation conditions that could otherwise melt them, and the chemistry process has to isolate highly pure actinium-225 from approximately 400 other isotopes.

RIT with actinium-225 can only become a reliable cancer-treatment option if the isotope's production can be scaled up to meet the increasing medical demand. Indeed, actinium-225 was originally developed for clinical research at Oak Ridge around 15 years ago, but practical applications remained limited by an insufficient supply. Fortunately, tri-lab scientists have successfully demonstrated the first major steps toward a large-scale, economically viable supply of the needed isotope. They estimate that once the full production pipeline is established—an investment of 5–10 years—it will take only a few days of beam time to match the present global annual production of actinium-225. Thereafter, accelerators at Los Alamos and Brookhaven, and chemical-processing capabilities at Oak Ridge, are planning to keep pace with the growing medical need.

So will it cure, or at least treat, different cancers? To find out, the tri-lab team has been collaborating with international clinical research leaders, building on years of research using the original Oak Ridge supply of actinium-225 on cancer-cell cultures and cancer-afflicted mice. In addition, human clinical trials performed to date show great effectiveness with a variety of actinium-225-



1. The patient receives an injection of the targeted radioisotope.

2. As the radioisotope circulates throughout the body, its attached antibody searches for a specific antigen found only on cancerous cells.

3. The radioisotope collects around cancerous cells and delivers radiation to those cells while minimizing damage to the body's healthy tissues.

4. Over time, the radioisotope decays, eliminating the radiation sources from the patient's body.

based drugs. One such drug under development to treat acute myeloid leukemia (AML), for example, has been tested on 18 patients at varying dosages and every time showed significant anti-leukemic activity with no toxicity to the patient. An expanded clinical trial is currently seeking additional AML patients to further assess the drug's effectiveness, and several others drugs based on actinium-225 are in the development pipeline as well.

"It looks really promising right now," Birnbaum says. "If FDA-approved clinical trials continue to pan out, then doctors can establish guidelines for actinium-225 treatments, what dosages to use, and so on. It's a real opportunity to deliver life-saving medicine in quantities that can have a tremendous impact."

"Through nuclear physics and chemistry," adds John. LDRD

—Craig Tyler

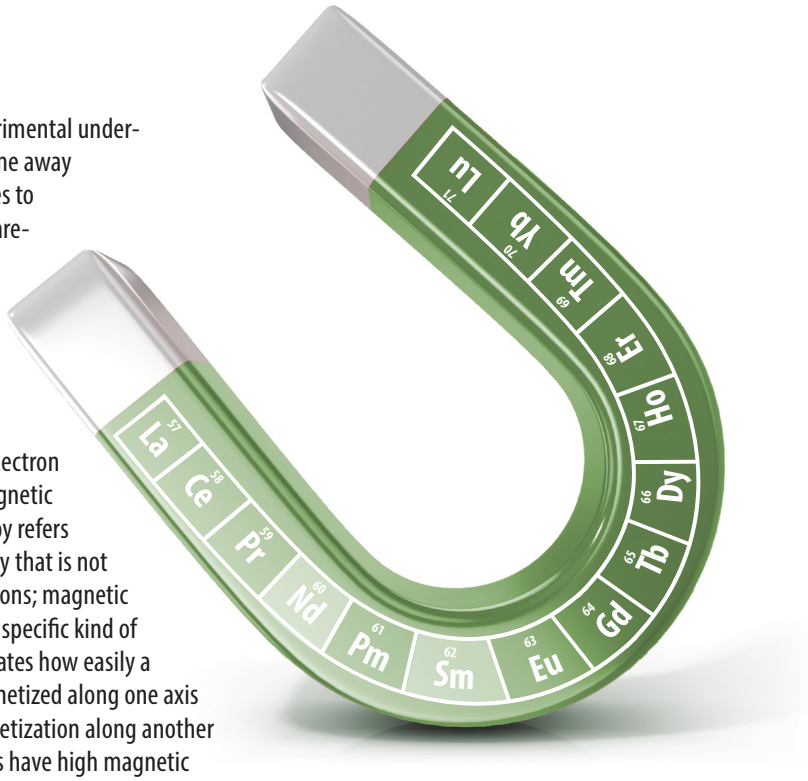
Mineral Magnetism

In addition to holding holiday cards to refrigerators well into the new year, magnets are also used in everyday items such as cell phones, children's toys, and shower curtains. Certain magnets garner the grandiose status of "strong magnets," and although the computing, medical imaging, and manufacturing industries all rely on strong magnets, by far the largest consumers of strong magnets are green technologies like wind energy and electric vehicles.

Strong magnets draw their defining strength from rare-earth minerals, such as neodymium and samarium. While these aren't exactly rare in nature, there is a scarcity in the United States stemming from limits on foreign sources, and each year, rare-earth minerals get harder to come by. Hence, the Laboratory is making a concerted effort to create rare-earth-free strong magnets.

A Los Alamos team led by materials physicist Joe Thompson wants to delineate what the crucial microscopic properties are that make a material magnetic. If the team can parse those out, it might be able to create new strongly magnetic materials without rare-earth elements.

To tackle this many-faceted problem, the team devised a two-pronged approach that combines quick computation with in-depth theoretical and experimental understanding. What it came away with was a set of rules to guide its search for rare-earth-free, strongly magnetic materials. The rules are very specific and have to do with ideal crystal structure, electron-electron interactions, and magnetic anisotropy. Anisotropy refers to a physical property that is not identical in all directions; magnetic anisotropy, then, is a specific kind of anisotropy that indicates how easily a material can be magnetized along one axis while resisting magnetization along another axis. Strong magnets have high magnetic anisotropy. Armed with the set of rules they devised, the scientists set about making and measuring materials they thought might pass muster.



To explore a material's physical properties, it is best to work with a single crystal of the material, in which the constituent atoms are arranged in a single ordered lattice. Synthesis of candidate magnetic materials in the necessary single-crystal solids proved time and cost restrictive. But the team quickly devised a workaround: because the materials were magnetic, they could be synthesized as polycrystals (much easier and faster to produce than single crystals), ground into a fine powder, then aligned by magnetic field while being glued back together into a single-crystal-like solid. This aligned-powder approach shaved months off of the time for initial analysis and helped whittle down the pool of candidates for further examination.

The material yttrium pentacobalt (YCo_5) is magnetic and free of rare-earth minerals, but it falls just short of the strength requirement to be classified as "very strong." However, YCo_5 is still a decent proxy for what the Los Alamos team is after. So, in concert with the aligned-powder effort, the team conducted a series of calculations and experiments aimed at a microscopic understanding of YCo_5's magnetism. By studying YCo_5 in depth, the team achieved two things: first, it proved the validity of its design-guiding rules, and second, it established a benchmark to which it could compare new candidate materials.

Out of hundreds of candidates, a single compound containing iron, germanium, and tellurium emerged as the front runner. Now, the time and cost to synthesize a true single crystal was easily justified. And that crystal has withstood ever-more rigorous probing of its magnetic nature.

But the new material is not quite ready for the mainstream. Since it becomes a strong magnet only at subzero temperatures, its immediate applications would be quite limited. Thompson is confident, however, that with further experiments and calculations, and by examining closely related compounds, there is promise for raising the temperature while maintaining the magnetism.

"The project was motivated by the need to replace rare-earth magnets in green technologies like wind turbines and electric cars," says Thompson. "We don't want dependence on those minerals to impede progress." Considering that a popular model of hybrid car uses more than two pounds of neodymium in each motor and that a typical wind turbine uses more than 100 pounds of it, the United States is consuming millions of pounds of neodymium per year. With green technologies gaining serious traction, the timing is perfect to find an alternative to endangered rare-earth magnets, allowing their use to go the way of whale oil and fade back into obscurity. LDRD

—Eleanor Hutterer